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| EXAMINER | |
|---|---|
| ROYDS, LESLIE A | |
| ART UNIT | PAPER NUMBER |
| 1614 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/626,037 | SCHERER, WARREN J. | |
| | Examiner | Art Unit | |
| | LESLIE A. ROYDS | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,11,12,34 and 36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,12,34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11 June 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1-2, 11-12, 34 and 36 are presented for examination.**

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed June 11, 2009 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 1-2, 11-12, 34 and 36 remain pending and under examination. Claim 35 is cancelled. Claims 1 and 36 are amended.

Applicant's arguments and Declaration under 37 C.F.R. 1.132 of Dr. Guy Webster, filed June 11, 2009, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

### *Claim Rejections - 35 USC § 103 (New Grounds of Rejection)*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 11-12, 34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (WO 02/36144; May 2002) in view of Gil et al. (U.S. Patent Application Publication No. 2003/0229088; Issued December 2003, Filed May 2002), citing to Burke et al. ("Preclinical Evaluation of Brimonidine", *Survey of Ophthalmology*, 41(Supp.1), 1996; S9-S18) as evidence, Wymenga et al.

("Management of Hot Flushes in Breast Cancer Patients", *Acta Oncologia*, 41(3); 2002:269-275) and Ito (EP 1069124 A1; 2001).

Arnold et al. teaches a medicament comprising one of more GnRH analogue compounds, optionally in combination with an estrogen or progestin compound, which may also be formulated in combination with at least one compound selected from, *inter alia*, alpha-adrenergic agonists (p.12, l.20-31). Arnold et al. further teaches that said medicament is useful for the treatment of side effects of ovarectomy or symptoms associated with reproductive senescence in female mammals (i.e., menopause; p.9, l.25-30), in particular, women (p.11, l.9-14), wherein such symptoms include vasomotor symptoms, especially hot flushes (p.10, l.10-14), and may be prepared in the form of creams or foams (p.15, l.6-12).

Arnold et al. fails to teach (1) the use of brimonidine or brimonidine tartrate as the alpha-adrenergic agonist, which has the selectivity properties recited in instant claims 1 and 34 (claims 1-2, 34 and 36); (2) topical administration of the composition locally to the site of the facial flushing (claims 1 and 36); or (3) the concomitant use of an additional agent as provided for in instant claims 11-12.

Gil et al. teaches known alpha-adrenergic agonists, including clonidine, brimonidine, tizanidine, etc. (p.1, para.[0009]) and salts thereof, including the tartrate salt (p.13, para.[0091]), and compositions thereof (p.13, para.[0096]) in dermatologically acceptable formulations, such as, e.g., a dermal patch, topical drops, creams, gels, or ointments, etc. (p.14, para.[0099]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the alpha-adrenergic agonist brimonidine or a salt thereof (such as, e.g., the tartrate salt of brimonidine) in the medicament disclosed by Arnold et al. as effective for the treatment of hot flashes that result from reproductive senescence in women because Gil et al. teaches that brimonidine (or its tartrate salt, for example) is one of a finite number of alpha-adrenergic agonists known in the prior art at the time of the invention to predictably function as agonists of alpha-adrenoreceptors. In other words, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ

any one of the known alpha-adrenergic agonists (which, as evidenced by Gil et al., included brimonidine or brimonidine tartrate) into this formulation of Arnold et al. with a reasonable expectation of success because (1) a person with ordinary skill in the art has good reason to pursue known options within his or her technical grasp and (2) Arnold et al. teaches the desirability of including such an alpha-adrenergic agonist into the disclosed GnRh analogue formulation for the treatment of hot flashes that result from reproductive senescence in women.

Moreover, though Gil et al. fails to explicitly teach that the disclosed brimonidine compound is at least two-fold to fifty-fold more selective (claim 1) or at least seven-fold to twelve-fold more selective (claim 34) for the alpha-2 adrenergic receptor as compared to clonidine, Burke et al. ("Preclinical Evaluation of Brimonidine", *Survey of Ophthalmology*, 41(Supp.1), 1996; S9-S18) is cited for its evidentiary teaching that brimonidine is known in the art to have a 7-fold to 12-fold greater selectivity for the alpha-2 adrenoreceptor as compared to clonidine (abstract). Accordingly, even though Gil et al. does not specifically disclose the degree of selectivity of brimonidine for the alpha-2 adrenoreceptor as compared to clonidine, Burke et al. provides the factual extrinsic evidence to show that this is a characteristic that is necessarily present in the teaching of the compound brimonidine.

Wymenga et al. teaches that menopausal flushing onset is abrupt and typically starts with a feeling of heat in the upper body that is generally associated with a visible reddening of the face (col.1, para.4, p.270). Wymenga et al. further teaches that administration of vitamin E (i.e., an antioxidant; see instant claims 11-12) in an amount of 800 I.U. per day to patients experiencing hot flushes demonstrated a significant reduction in flushing, which, though on average was only a reduction in one flushing incident per day, was still suggested for use in treating hot flushes due to its non-toxic and inexpensive properties, as well as the fact that it is widely available (col.2, para.2, p.272).

Ito teaches compounds and pharmaceutical compositions containing said compounds in an effective amount and a pharmaceutically acceptable carrier (p.5, para.[0026]), and are useful for the

treatment of disorders or medical conditions, such as inflammatory diseases (p.2, para.[0001]), wherein the condition to be treated is, *inter alia*, vasomotor disturbances including hot flushes (p.5, para.[0027]). Ito teaches that the compounds should be administered topically when treated inflammatory conditions of the skin, preferably by way of creams, gels, pastes, ointments, etc. (p.14, para.[0076]).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to apply the cream or foam formulation of Arnold et al. topically to the site of the facial flushing in a patient experiencing menopausal-related hot flashes because (1) menopause-associated hot flashes result in visible reddening of the face, as evidenced by Wymenga et al., (2) topical treatment of inflammatory conditions of the skin, such as hot flushes, should be treated topically with, e.g., creams, pastes, etc., as evidenced by Ito, and (3) the skilled artisan would have recognized the advantage to directly treating the area of flushing with a topical formulation effective to treat such flushing by applying it directly to the affected area of skin, such as, e.g., directly to the face to treat facial flushing resulting from menopausal hot flashes, absent factual evidence to the contrary. Such a person would have been motivated to do so in order to treat the affected area while minimizing exposure of unaffected areas to the pharmacologic formulation.

Furthermore, one of skill in the art would have also found it *prima facie* obvious to combine the formulation of Arnold et al. in view of Gil et al. with the vitamin E compound in light of the disclosure of Wymenga et al. because Wymenga et al. teaches the activity of vitamin E in effecting a significant reduction in the incidence of menopausal hot flushes and, thus, the cutaneous flushing associated therewith. Motivation to administer both compounds/compositions together flows logically from the very fact that each discrete agent was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two agents, when combined, would have, at minimum, additive, if not synergistic, effects in reducing the incidence of menopausal hot flushes (and the cutaneous flushing that results from the same) when combined.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

***Conclusion***

Rejection of claims 1-2, 11-12, 34 and 36 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

August 12, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614